

# Journal of Contemporary Health Law & Policy (1985-2015)

---

Volume 25 | Issue 1

Article 9

---

2008

## Switching to Generic: The Need for Physician and Patient Consent When Substituting Antiepileptic Medication

Evan H. Langdon

Follow this and additional works at: <https://scholarship.law.edu/jchlp>

---

### Recommended Citation

Evan H. Langdon, *Switching to Generic: The Need for Physician and Patient Consent When Substituting Antiepileptic Medication*, 25 J. Contemp. Health L. & Pol'y 166 (2009).

Available at: <https://scholarship.law.edu/jchlp/vol25/iss1/9>

This Comment is brought to you for free and open access by CUA Law Scholarship Repository. It has been accepted for inclusion in Journal of Contemporary Health Law & Policy (1985-2015) by an authorized editor of CUA Law Scholarship Repository. For more information, please contact [edinger@law.edu](mailto:edinger@law.edu).

# SWITCHING TO GENERIC: THE NEED FOR PHYSICIAN AND PATIENT CONSENT WHEN SUBSTITUTING ANTIEPILEPTIC MEDICATION

*Evan H. Langdon\**

The amount Americans spend each year on prescription drugs has increased dramatically from 120 billion dollars in 1999 to 200 billion dollars in 2005.<sup>1</sup> Generic drugs are currently estimated to save consumers twenty billion dollars a year<sup>2</sup> and can save consumers close to fifty percent on their daily medication needs if they choose generic drugs instead of brand name drugs.<sup>3</sup> Congress and many federal agencies support the increased use of generic drugs as an effective way to lower health care costs.<sup>4</sup> Health care authorities worldwide are implementing policies that encourage the use of generic drugs as a simple and effective way to control the cost of

---

\* J. D. Candidate May 2009, The Catholic University of America, Columbus School of Law; B.S. Mechanical Engineering 2002, Villanova University. The author wishes to thank his wife, Jennifer, for her support and encouragement. Special thanks to Bill Murphy, Director of State Government Relations, Epilepsy Foundation, for his expert knowledge and guidance.

1. Kate Kellogg, *There's Good News, Bad News in Drug Development*, THE UNIVERSITY RECORD, Sept. 18, 2000, [http://www.ur.umich.edu/0001/Sep18\\_00/3.htm](http://www.ur.umich.edu/0001/Sep18_00/3.htm); KAISER FAMILY FOUND., PRESCRIPTION DRUG TRENDS (2007), [http://www.kff.org/rxdrugs/upload/3057\\_06.pdf](http://www.kff.org/rxdrugs/upload/3057_06.pdf).

2. Jonathan D. Rockoff, *Cost of Medicine Could Increase: Brand-Name Drugmakers Target Generic Prescriptions*, BALTIMORE SUN, June 17, 2008, at 1A.

3. See FDA, CTR. FOR DRUG EVALUATION & RESEARCH, SAVINGS FROM GENERIC DRUGS PURCHASED AT RETAIL PHARMACIES (2004), <http://www.fda.gov/cder/consumerinfo/savingsfromgenericdrugs.htm>; see also Epilepsy Foundation, Generic Drugs: A Welcome Savings ... But Are They Right for All?, <http://www.epilepsyfoundation.org/generics/index.html> (last visited Oct. 11, 2008) [hereinafter Generic Drugs] (stating generic drugs currently save consumers eight to ten billion dollars a year at retail pharmacies).

4. Generic Drugs, *supra* note 3.

medication.<sup>5</sup> Although substitution of cheaper generic alternatives can result in significant cost savings, generic substitution can create risks for some patients, especially for epileptic patients.

Epilepsy is a neurological condition that produces brief disturbances in the normal electrical functions of the brain that affect a variety of mental and physical functions.<sup>6</sup> The condition occurs when the normal brain function that delivers tiny electrical charges between nerve cells is interrupted by an intense burst of electrical energy.<sup>7</sup> Due to the unique nature of epilepsy, there are various reasons that a seizure may occur and different parts of the brain may be affected in different ways, making treatment exceptionally difficult. In fact, for seventy percent of people living with epilepsy or seizures, the cause of the condition is unknown.<sup>8</sup> A cure for epilepsy does not presently exist;<sup>9</sup> however, many people living with epilepsy can prevent seizures by regularly taking medication and actively communicating with their physician.<sup>10</sup> More than three million Americans are treated for epilepsy,<sup>11</sup> most commonly with antiepileptic medication.<sup>12</sup> Antiepileptic

---

5. G. Kramer et al., *Current Approaches to the Use of Generic Antiepileptic Drugs*, 11 EPILEPSY & BEHAV. 46, 46 (2007).

6. Epilepsy Foundation, What is Epilepsy?, <http://www.epilepsyfoundation.org/about> (last visited Oct. 11, 2008) [hereinafter What is Epilepsy?] (listing symptoms ranging from “convulsions and loss of consciousness to some that are not always recognized as seizures by the person experiencing them or by health care professionals: blank staring, lip smacking, or jerking movements of arms and legs.”).

7. *Id.*

8. Epilepsy Foundation, Seizures and Syndromes, <http://www.epilepsyfoundation.org/about/types/index.cfm> (last visited Oct. 11, 2008) (The most frequent causes in the remaining thirty percent are brain tumor or stroke, head trauma, poisoning, infection, and maternal injury).

9. Epilepsy Foundation, Treatment Options: Medications, <http://www.epilepsyfoundation.org/about/treatment/medications> (last visited Oct. 11, 2008) [hereinafter Treatment Options].

10. *Id.*

11. What is Epilepsy?, *supra* note 6; see National Conference of State Legislatures: The Forum of America’s Ideas, Condition-specific Drug Substitution Legislation: Epilepsy, <http://www.ncsl.org/programs/health/rx-substitution08.htm> (last visited Oct. 11, 2008) [hereinafter Forum of America’s Ideas] (stating “[a]pproximately 3.2 million Americans suffer from Epilepsy, including 40% who are women of childbearing age.”).

drug therapy can be highly effective; however, “accurate prediction of an individual’s response to medication is not possible.”<sup>13</sup>

This article will demonstrate that the measures currently in place to protect epileptic patients are inadequate. With generic versions of four major brand name antiepileptic drugs set to enter the market by 2010, pharmacists should be required to obtain the notification and consent of both the patient and the patient’s physician before substituting any antiepileptic drug for another antiepileptic drug.

In order to place the article’s argument in context, Part I provides background information related to the development of generic drugs. Part I also explains the approval process for generic drugs, as well as the treatment of epilepsy with antiepileptic drug therapy. Part II explains why substitution of generic drugs for brand name drugs is encouraged and how the substitution of antiepileptic drugs may be unavoidable. Moreover, Part II shows how different groups of epileptic patients are affected by substitution and who ultimately bears the burden of generic substitution of antiepileptic drugs. Part III analyzes state legislation that restricts generic substitution of antiepileptic drugs and demonstrates why it fails to protect people living with epilepsy. Part IV provides a proposed statute that requires notification and consent of the patient and the patient’s physician prior to substitution of an antiepileptic medication. The article concludes in Part V with a look at the potential means for protecting epileptic patients from unprompted changes in treatment.

## I. THE PROBLEMS ASSOCIATED WITH THE GENERIC SUBSTITUTION OF ANTIEPILEPTIC DRUGS

### *A. Developing Brand Name and Generic Drugs*

The average cost to drug companies in researching, developing, and creating a new Food and Drug Administration (FDA) approved drug is 802 million dollars.<sup>14</sup> This cost can reach nearly 1.7 billion dollars when

---

12. Treatment Options, *supra* note 9.

13. Epilepsy Foundation, Drug Formularies and the Availability of Antiepileptic Medications, <http://www.epilepsyfoundation.org/advocacy/govaff/pp1.cfm> (last visited Oct. 11, 2008) [hereinafter Drug Formularies].

14. PhRMA, WHAT GOES INTO THE COST OF PRESCRIPTION DRUGS? ... AND OTHER QUESTIONS ABOUT YOUR MEDICINES 2 (2005), [http://www.phrma.org/files/Cost\\_of\\_Prescription\\_Drugs.pdf](http://www.phrma.org/files/Cost_of_Prescription_Drugs.pdf) [hereinafter PhRMA] (citing J.A. DiMasi, R.W. Hansen & H.G. Grabowski, *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 151-85 (2003)).

factoring in failed drug candidates.<sup>15</sup> The majority of the cost is attributed to the FDA's comprehensive pre-market approval process that is required by the Federal Food, Drug, and Cosmetic Act (FDCA).<sup>16</sup> The FDA approval process averages 8.2 years,<sup>17</sup> increasing the estimated time to discover and develop a new drug to twelve to fifteen years.<sup>18</sup> The Patent Act provides drug companies the right to patent new drugs and offers market exclusivity to sell and market a new drug for a term of twenty years.<sup>19</sup> The lengthy FDA approval process effectively shortens the patent term,<sup>20</sup> thereby shortening the period of time during which research and development costs can be recovered. The drug companies then seek to recover these costs from consumers through higher prices.<sup>21</sup>

Generic versions of drugs can actively participate in domestic and global markets once the patent rights of a brand name drug expire.<sup>22</sup> Generic drugs are sold at cheaper prices because manufacturers take advantage of a brand name drug's existing research and development.<sup>23</sup> Congress passed the

---

15. Ann M. Thayer, *Blockbuster Model Breaking Down: Pharma Industry Reaches New Sales Peak, Despite Rising Costs and Bigger Challenges for Drug R&D*, MODERN DRUG DISCOVERY 23, 23 (2004).

16. Thomas Noud & Paul Meiklejohn, *The Developing Law of Pharmaceutical Patent Enforcement*, 87 J. PAT. & TRADEMARK OFF. SOC'Y 921, 921 (2005).

17. *Id.*

18. PHRMA, *supra* note 14, at 2.

19. 35 U.S.C. § 154(a)(1) (2000) ("Every patent shall . . . grant to the patentee . . . the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States or importing the invention . . . [and] the right to exclude . . . products made by that process, referring to the specification for the particulars thereof."); 35 U.S.C. § 154(a)(2) (2000) (limiting a patent term to a period of twenty years from the date of filing of the patent application).

20. Noud & Meiklejohn, *supra* note 16, at 921.

21. Allison Ladd, *Integra v. Merck: Effects on the Cost and Innovation of New Drug Products*, 13 J.L. & POL'Y 311, 312 (2005).

22. *Id.*

23. *Id.* at 312-13 (stating patent laws require full disclosure of patented inventions thereby allowing generic drug manufacturers to obtain necessary information on submissions of brand name drugs in order to develop and manufacture generic versions).

Drug Price Competition and Patent Term Restoration Act of 1984 as a means of controlling rising drug prices.<sup>24</sup> Commonly referred to as the “Hatch-Waxman Act,” this law simplified FDA approval of generic drugs by permitting drug manufacturers to obtain FDA approval of bioequivalent versions of a brand name drug through an Abbreviated New Drug Application (ANDA).<sup>25</sup>

*B. The FDA’s Criteria for Bioequivalent Generic Drugs*

In order to gain approval, the generic drug company must show bioequivalence of the generic and brand name drug.<sup>26</sup> Bioequivalence is shown when the active ingredient in the generic drug has an equivalent release and an equivalent rate and extent of absorption in comparison to the

---

Patent law, however, prohibited generic drug companies from engaging in the premarket approval process required by the FDA until after the brand name patent had expired. *Id.* at 313 (citing *Roche Prod. Inc. v. Bolar Pharm. Co.*, 733 F.2d 858 (Fed. Cir. 1984) (holding that performance of experiments to derive FDA required test data, conducted with a view towards the adaptation of the patented invention to the experimenter’s business is a violation of patentee’s right to exclude others from using his patented invention)). This effectively extended the patent rights of the brand name drug company. Noud & Meiklejohn, *supra* note 16, at 922.

24. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984); Noud & Meiklejohn, *supra* note 16, at 922; Ladd, *supra* note 21, at 313.

25. Noud & Meiklejohn, *supra* note 16, at 922. The Hatch-Waxman Act also included a “safe harbor” provision excluding from patent infringement “all activities related to the gathering of information required for compliance with federal laws that regulate drugs.” Ladd, *supra* note 21, at 314. The “safe harbor” provision allows generic companies to engage in the FDA approval process without infringing on the brand name drug’s patent rights to enable them to access the market more quickly. *Id.* at 314-15 (quoting *Integra Life Sciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 867 (Fed. Cir. 2003) (holding “that the safe harbor does not reach ‘any exploratory research that may rationally form a predicate for future clinical tests.’”)). In effect, this decision limits the safe harbor protection to “generic drug manufacturers that seek FDA approval for products that compete with existing brand name drugs.” *Id.* at 315.

26. P. Crawford et al., *Are There Potential Problems with Generic Substitutions of Antiepileptic Drugs? A Review of the Issues*, 15 SEIZURE 165, 166 (2006), available at <http://www.sciencedirect.com/science/journal/10591311> (follow “Volume 15 (2006)” hyperlink; then follow “Volume 15, Issue 3” hyperlink; then follow “PDF 167K” hyperlink under number 6).

active ingredient in the brand name drug product.<sup>27</sup> The “concept of bioequivalence is . . . that . . . if a drug product contains a drug substance that is chemically identical and is delivered . . . at the same rate and extent as another drug product, then it is equivalent and can be substituted for that drug product.”<sup>28</sup> A variety of methods to determine bioequivalence can be used depending on the type of drug tested.<sup>29</sup> The FDA’s position is that “[i]f one therapeutically equivalent drug is substituted for another, the physician, pharmacist, and patient have FDA’s assurance that the physician should see the same clinical results and safety profile.”<sup>30</sup>

Generic drugs must have the same *active* ingredient as their brand name equivalent; however, they do not need to have the same *inactive* ingredient.<sup>31</sup> The FDA does not require exact equivalence. Current FDA guidelines allow bioequivalence of a generic drug to range between 80% and 125% when compared to the brand name drug.<sup>32</sup> This means that despite the effects of inactive ingredients present in a generic drug, the generic drug must only demonstrate that the active ingredient is delivered at a rate that is between 80% and 125% when compared to the brand name drug.<sup>33</sup> Based on the approval process for generic drugs, exact equivalence is an impossible bar to

---

27. FDA, CTR. FOR DRUG EVALUATION & RESEARCH, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS viii (28th ed. 2008), *available at* <http://www.fda.gov/cder/orange/obannual.pdf> [hereinafter ORANGE BOOK]; 21 C.F.R. § 320.23 (2008).

28. ORANGE BOOK, *supra* note 27, at viii.

29. *Id.*; 21 C.F.R. § 320.24 (2008).

30. Letter from Roger L. Williams, M.D., Deputy Center Director for Pharmaceutical Science, Ctr. for Drug Evaluation & Research, to Carmen A. Catizone, Executive Director/Secretary, National Ass’n of Boards of Pharmacy (Apr. 16, 1997), <http://www.fda.gov/cder/news/ntiletter.htm>; ORANGE BOOK, *supra* note 27, at vii (“FDA classifies as therapeutically equivalent those products that . . . are approved as safe and effective . . . are pharmaceutical equivalents . . . are bioequivalent . . . are adequately labeled . . . [and] are manufactured in compliance with [approved] regulations.”).

31. Andrew N. Wilner, *Therapeutic Equivalency of Generic Antiepileptic Drugs: Results of a Survey*, 5 EPILEPSY & BEHAV. 995, 997 (2004).

32. ORANGE BOOK, *supra* note 27, at ix.

33. *Id.*

clear because there are minor variations in the way people absorb drugs.<sup>34</sup> In addition, the generic drug may be manufactured differently, and this process can influence dissolution rates in the digestive tract, and therefore the absorption of the drug.<sup>35</sup> The FDA has upheld a long-standing position requiring major clinical evidence to demonstrate that a prior approved generic drug is not bioequivalent.<sup>36</sup> Without a showing of data to the contrary, the FDA will conclude that the difference is too small to have a substantial impact on patients.<sup>37</sup>

### C. *The Inherent Problems with the FDA Approval Process*

The FDA approval process requires a generic drug to contain the same active ingredient as the brand name drug, but allows for different inactive ingredients as long as bioequivalence falls within the acceptable range of 80% to 125%.<sup>38</sup> Once a generic drug is approved, the FDA requires extensive evidence to rebut the presumption of bioequivalence, and courts will show deference to the FDA's decision.<sup>39</sup> However, the acceptable

---

34. Sarah Rubenstein, *Industry Fights Switch to Generics for Epilepsy*, WALL ST. J., Jul. 13, 2007, at A1.

35. Kramer et al., *supra* note 5, at 48 (stating the differences in the “manufacturing process used, in the excipients with which the active principle is associated in the final drug product and the appearance of the drug product (shape, color, or both) . . . may influence dissolution rates in the gastrointestinal tract and, thus, absorption of the drug substance and overall pharmacokinetics.”).

36. 21 C.F.R. § 320.33 (2008) states that:

The Commissioner of Food and Drugs shall consider . . . well-documented evidence [that] pharmaceutical equivalents . . . are not or may not be bioequivalent drug products [based on] (a) Evidence from well-controlled clinical trials or controlled observations in patients that such drug products do not give comparable therapeutic effects. (b) Evidence from well-controlled bioequivalence studies that such products are not bioequivalent drug products. (c) Evidence that the drug products exhibit a narrow therapeutic ratio . . . .

*Id.*

37. Rubenstein, *supra* note 34, at A1.

38. Wilner, *supra* note 31, at 997; ORANGE BOOK, *supra* note 27, at vi.

39. 21 C.F.R. § 320.33 (2008); *see* Warner-Lambert Co. v. Shalala, 202 F.3d 326, 331 (D.C. Cir. 2000) (upholding the FDA's decision to approve a new generic anti-



bioequivalence range set by the FDA was not based on conclusive evidence, but rather was “based on the opinions of FDA medical experts.”<sup>40</sup> Considering that the parameters for bioequivalence were originally set by opinions of “medical experts” and not fact-based evidence, it is irrational to require a high level of conclusive evidence to show generic alternatives are not bioequivalent. Other medical experts in the United States and around the world have provided opinions regarding the flawed nature of the bioequivalence standard<sup>41</sup> and “recommend that doctors give explicit approval for switches.”<sup>42</sup>

The FDA’s approval process has another intrinsic flaw: the test for bioequivalence is conducted on a small number of healthy adult volunteers, “usually 24 to 36 adults.”<sup>43</sup> One major problem with testing a small, limited sample of healthy individuals is that the drug will eventually be used to treat a larger number of patients whose existing illnesses or other treatments may affect drug pharmacology.<sup>44</sup> A second major problem is that establishing

---

seizure medication on the premise that it was therapeutically equivalent to the drug Dilantin).

40. Wilner, *supra* note 31, at 997. These opinions are based on [t]he statistical methodology for analyzing . . . bioequivalence . . . called the two one-sided test procedure. Two situations are tested with this statistical methodology. The first of the two one-sided tests determines whether a generic product (test), when substituted for a brand-name product (reference) is significantly less bioavailable. The second of the two one-sided tests determines whether a brand-name product when substituted for a generic product is significantly less bioavailable . . . difference of greater than 20% for each of the above tests was determined to be significant, and therefore, undesirable for all drug products.

ORANGE BOOK, *supra* note 27, at ix.

41. See, e.g., Wilner, *supra* note 31, at 995; Crawford et al., *supra* note 26, at 167-69; Kramer et al., *supra* note 5, at 48; Dominic C. Heaney & Josemir W. Sander, *Antiepileptic Drugs: Generic Versus Branded Treatments*, 6 LANCELOT NEUROLOGY 465, 467 (2007).

42. Rubenstein, *supra* note 34, at A1.

43. ORANGE BOOK, *supra* note 27, at viii; 21 C.F.R. § 320.24 (2008); Heaney & Sander, *supra* note 41, at 466; Crawford et al., *supra* note 26, at 169.

44. Heaney & Sander, *supra* note 41, at 466; Pharmacology is “the properties and reactions of drugs esp. in relation to their therapeutic value.” MERRIAM-WEBSTER’S COLLEGIATE DICTIONARY 868 (10th ed. 2001).

bioequivalence in a group of healthy individuals is not synonymous with establishing bioequivalence for an individual patient. For example, individual epileptic patients respond to antiepileptic drugs in different ways, making it difficult to establish bioequivalence for the group as a whole.<sup>45</sup> The third major problem is that test groups for bioequivalence usually do not include children and the elderly, “two groups that make up a considerable portion of patients receiving antiepileptic drugs.”<sup>46</sup> Lastly, many patients take more than just one drug. The presence of multiple medications can affect how the drugs react in the patient. For example, an epileptic patient may take more than one antiepileptic medication and other medications that can affect the drug’s absorption rate and behavior.<sup>47</sup> Currently, studies have not been conducted and empirical evidence is not available on the bioequivalence of antiepileptic medications in multiple-medicated epileptic patients.<sup>48</sup> Moreover, a brand name antiepileptic drug made by a single company has only one brand and method of manufacturing, but a generic antiepileptic drug can be made by multiple companies and by multiple manufacturing methods within FDA guidelines.<sup>49</sup> Due to these possible differences, as well as the individual characteristics of each patient, the bioequivalence of different antiepileptic medications cannot be presumed.

#### *D. Treating Epileptic Patients with Antiepileptic Drugs*

Close to seventy percent of epileptic patients can be seizure-free if they maintain an appropriate drug and dose regimen.<sup>50</sup> Obtaining freedom from seizures requires “rigid adherence” to a carefully adjusted drug regimen and close monitoring by the patient’s physician.<sup>51</sup> Monitoring patients is

---

45. See Heaney & Sander, *supra* note 41, at 465; see Crawford et al., *supra* note 26, at 168.

46. Kramer et al., *supra* note 5, at 49.

47. *Id.*

48. *Id.*

49. Steven C. Schachter, Chair, Epilepsy Found. Advisory Comm. on Generic Antiepileptic Drugs, Address at Epilepsy Foundation’s Annual Leadership Conference: Protecting Patient Access to Safe and Effective Epilepsy Medications (Sept. 28, 2007).

50. Heaney & Sander, *supra* note 41, at 465.

51. *Id.* (drug regimens usually involve taking medication up to three times a day for many years or for life); Crawford et al., *supra* note 26, at 168.

difficult for a number of reasons. Wide variations in each person's response to treatment, for example, have led physicians to recommend that changes or substitutions to prescribed regimens be made over several weeks or months.<sup>52</sup> Due to the long titration process to determine the proper dosage, many physicians and patients are reluctant to make changes once stability is attained.<sup>53</sup>

There are three main groups of epileptic patients: patients initiating antiepileptic drug therapy, patients controlled by antiepileptic drug therapy, and patients who are not well-controlled, or considered high-risk patients.<sup>54</sup> The goal for each group is to establish long-term stable treatment and the avoidance of seizures once a patient has become seizure-free.<sup>55</sup> Abrupt changes in a patient's medication can result in a "breakthrough seizure," a seizure that "occurs unexpectedly while on drug therapy."<sup>56</sup> After a period of stability, the impact of a single seizure can have serious social implications, such as the loss of one's driver's license or employment.<sup>57</sup> Personal implications can include physical injuries or the loss of self-esteem.<sup>58</sup> In addition, "the risk of death in patients with uncontrolled seizures is higher than in patients with controlled seizures."<sup>59</sup> These external factors are unique to treating epilepsy, as changing medications designed to

---

52. Heaney & Sander, *supra* note 41, at 465; Crawford et al., *supra* note 26, at 168.

53. Crawford et al., *supra* note 26, at 168.

54. Kramer et al., *supra* note 5, at 50-51.

55. Crawford et al., *supra* note 26, at 167.

56. Epilepsy Foundation, Terms, <http://www.epilepsyfoundation.org/generics/glossary.html> (last visited Oct. 11, 2008).

57. Crawford et al., *supra* note 26, at 167 (listing loss of driver's license and loss of employment as social implications).

58. *Id.* (listing risk of injury and loss of self-esteem as personal implications). See also Susan Spencer, *Epilepsy: Clinical Observations and Novel Mechanisms*, 6 THE LANCET NEUROLOGY 14 (2006) (suggesting people diagnosed with epilepsy are three times more likely to commit suicide than the general population).

59. Crawford et al., *supra* note 26, at 167.

treat other conditions does not present the same personal and social consequences.<sup>60</sup>

Antiepileptic drugs have a narrow therapeutic index, meaning there is a small difference between a high dosage that is toxic and a low dosage that is ineffective.<sup>61</sup> A narrow therapeutic index combined with the wide variation in responses to treatment among individual patients creates the risk of different therapeutic responses to antiepileptic drugs defined as bioequivalent.<sup>62</sup> Generic drugs are only tested for bioequivalence when compared to brand name counterparts; they are not tested for bioequivalence when compared to other generic drugs.<sup>63</sup> The current bioequivalence standard set by the FDA “raises the possibility that the bioequivalence of different [generic drugs] may fall outside the acceptable range” when compared to each other.<sup>64</sup> Patients may be switched from one generic drug whose bioequivalence is at the top of the acceptable range to a different generic drug whose bioequivalence is at the bottom of the acceptable range.<sup>65</sup> The problem is not simply switching from a brand name antiepileptic drug to a generic antiepileptic drug; the same problem is also present when switching from a generic drug to another generic drug, or from a generic drug back to a brand name drug.

---

60. *See id.*

61. *Id.* An inadequate amount of the active ingredient will not affect the patient, whereas too much of the active ingredient can cause adverse effects. In addition to possible breakthrough seizures, possible toxic effects include sedation, lethargy, cognitive and coordination impairment, rashes and gastrointestinal problems. Schachter, *supra* note 48.

62. Crawford et al., *supra* note 26, at 168-69 (listing factors that increase the likelihood of problems with generic substitution: low water solubility, narrow therapeutic range, and nonlinear pharmacokinetics).

63. Kramer et al., *supra* note 5, at 48.

64. *Id.*

65. Crawford et al., *supra* note 26, at 169; *see also* Kramer et al., *supra* note 5, at 48 (explaining “if generic form A provides a peak plasma concentration of 124% of the reference [drug], and generic form B provides concentrations of 81% of the reference [drug], then both are considered to be bioequivalent to the reference [drug]. However, the plasma concentrations obtained in B will only be 65% of those attained in A.”).

## II. THE SWITCH TO GENERIC ANTIEPILEPTIC DRUGS

### A. Requiring Epileptic Patients to Switch to Generic Antiepileptic Drugs

Due to rising healthcare costs, most prescription drug purchases in the United States are paid for, at least in part, by employer-sponsored health insurance plans, health maintenance organizations (HMOs), or by government programs like Medicaid and Medicare.<sup>66</sup> It has become commonplace for health program providers to establish drug formularies.<sup>67</sup> A drug formulary is a list of approved medications that are subsidized in part by a particular plan.<sup>68</sup> Drug formularies were developed to control spending on prescription drugs.<sup>69</sup> Incentive-based formularies place brand name drugs on a higher cost tier than generic drugs.<sup>70</sup> This formulary creates an incentive to choose prescription drugs from the lower cost tier, generating savings for the health plan.<sup>71</sup>

Another type of drug formulary is the Medicaid formulary, which does not have tiers or incentives.<sup>72</sup> The drugs listed on the Medicaid formulary are

---

66. *Abbott Lab. v. Andrx Pharm., Inc.*, No. C 1490, 2005 WL 1323435, at \*15 (N.D. Ill. June 3, 2005); Drug Formularies, *supra* note 13; *see generally* Jack Hoadley, Elizabeth Hargrave, Katie Merrell, Juliette Cubanski & Tricia Neuman, Benefit Design and Formularies of Medicare Drug Plans: A Comparison of 2006 and 2007 Offerings, A First Look (2006), available at <http://www.kff.org/medicare/upload/7589.pdf>.

67. Drug Formularies, *supra* note 13.

68. *Abbott Lab.*, 2005 WL 1323435, at \*15.

69. Drug Formularies, *supra* note 13.

70. Cindy Parks, *Incentive-Based Formularies*, 349 NEW ENGL. J. MED. 2186, 2186 (2003). Incentive-based formularies are typically divided into three tiers. The first tier comprises low cost generic products, the second tier comprises "preferred branded" products and the third tier comprises "non-preferred branded" products. Patients are required to pay more for drugs listed on a higher tier than for a drug of the same price listed on a lower tier. *Abbott Lab.*, 2005 WL 1323435, at \*15.

71. Parks, *supra* note 70, at 2186 ("[T]he amount of copayments depend[s] on the type of drug prescribed; the contracts among the insurer, the manufacturer, and the pharmacy; and the price differential between the selected drug and reasonable low-cost substitutes.").

72. *Abbott Lab.*, 2005 WL 1323435, at \*15.

covered by the program.<sup>73</sup> If a drug is not listed on the formulary, the patient must pay for its cost out-of-pocket.<sup>74</sup> Medicare's programs include both tiered and non-tiered formularies.<sup>75</sup> When a brand name medication becomes available in the generic form, providers add the generic to their formulary on the lowest-cost tier and then move the branded product to a higher tier.<sup>76</sup> Some plans, such as Medicaid, "remove the branded drug from their formulary altogether."<sup>77</sup> Step-therapy formularies are two-step programs that require the use of a generic drug first, and then a preferred brand name drug, before the program will cover a non-preferred brand name drug.<sup>78</sup> Referred to as the "fail-first" formulary,<sup>79</sup> the program stipulates that the "[u]se of non-preferred brand products without prior use of generic and preferred brand products will require Prior Authorization (PA)."<sup>80</sup> With regard to epilepsy, "'failure' means having a seizure."<sup>81</sup>

All fifty states permit pharmacists, under certain circumstances, to substitute a generic drug even though a physician has prescribed a brand

---

73. *Id.*

74. *Id.* If a doctor prescribes a drug not listed on the Medicaid patient formulary, "the patient must pay the entire cost out-of-pocket." *Id.*

75. *See generally* Hoadley et al., *supra* note 66.

76. *Abbott Lab.*, 2005 WL 1323435, at \*15.

77. *Id.*

78. CIGNA PHARMACY MANAGEMENT, PARTICIPATING PHARMACY NEWSLETTER (2007), available at [http://www.cigna.com/customer\\_care/healthcare\\_professional/pharmacy/newsletter/200708.pdf](http://www.cigna.com/customer_care/healthcare_professional/pharmacy/newsletter/200708.pdf) [hereinafter CIGNA].

79. JEFFREY CROWLEY, DEB ASHNER & LINDA ELAM, THE KAISER COMM'N ON MEDICAID AND THE UNINSURED, MEDICAID OUTPATIENT PRESCRIPTION DRUG BENEFITS: FINDINGS FROM A NATIONAL SURVEY, iii (2003), available at <http://www.kff.org/medicaid/4164.cfm> (follow "report" hyperlink).

80. CIGNA, *supra* note 78.

81. Eric Hargis, President and Chief Executive Officer, Epilepsy Found., Remarks at American Medical Association Media Briefing on Antiepileptic Drug Guidelines (Apr. 26, 2004), transcript available at <http://www.epilepsyfoundation.org/aboutus/pressroom/pr20040426b.cfm>.

name drug.<sup>82</sup> If a generic drug is available, thirty states mandate the substitution.<sup>83</sup> The states permitting substitution encourage the use of generics by “aggressively managing the Medicaid prescription drug benefit.”<sup>84</sup> In comparison to generic drug policies in other countries, only France and the United Kingdom have outlawed generic substitution of brand name drugs.<sup>85</sup>

Not all substitutions are due to state requirements or health care provider incentives. The market for particular generic drugs may not be flooded with suppliers.<sup>86</sup> Recent trends show that companies that have traditionally produced brand name products now produce generic drugs directly, or have wholly owned subsidiaries that produce them.<sup>87</sup> This arrangement stifles the anticipated competition between generic drug producers and brand name

---

82. Thomas P. Christensen et al., *Drug Product Selection: Legal Issues*, 41 J. AM. PHARM. ASS'N 868, 869 (2001), available at <http://www.medscape.com> (register for the site; then search “Drug Product Selection Legal;” then follow “Drug Product Selection: Legal Issues” hyperlink).

83. CROWLEY, ASHNER & ELAM, *supra* note 79, at iv (noting “30 of 43 states reporting in 2003” as compared to 16 of 44 states in 2000).

84. *Id.* at iii-vi (“Nearly half of the states (18 of 43 states reporting in 2003) operate [Preferred Drug Lists]” and “[t]hirty-five of 43 states in 2003 reported cost sharing for prescription drugs . . . .” In addition, thirty of forty-three states “track ‘high-cost’ users of prescription drugs” and twenty-four of forty-three states “track ‘high-prescribing’ physicians . . . .”).

85. Lisa S. Haskins et al., *Patient and Physician Reactions to Generic Antiepileptic Substitution in the Treatment of Epilepsy*, 7 EPILEPSY & BEHAV. 98, 99 (2005). Pharmacists in Germany are required to substitute a generic drug when the patent of a brand name drug has lost protection or when there is a cheaper generic available. Other countries, including Spain and Canada, do not require substitution when a cheaper generic is available, but pharmacists are not required to consult a physician in order to substitute a generic. *Id.*

86. Heaney & Sander, *supra* note 41, at 467.

87. *Id.* (noting that Novartis, the world’s sixth largest producer of brand name drugs, is also one of the world’s largest producers of generic drugs); see also Kramer et al., *supra* note 5, at 48 (stating that when a drug company makes a generic copy of their own drug, a common manufacturing process is used and the generic copy is often identical to the brand name drug. The problems associated with generic substitution are not at issue for “manufacturer’s own” generics).

drug producers. There are a small number of antiepileptic drug producers who rely on the profitability of individual drugs.<sup>88</sup> These drug manufacturers are under no obligation to continue producing drugs if their profits decrease.<sup>89</sup> As a result, a patient who is prescribed the cheapest generic drug may be forced to switch between brand name drugs and different forms of generic drugs as drug producers enter and exit the market.<sup>90</sup> Supply of antiepileptic drugs is not guaranteed and patients may be subject to many switches over time. It is important that these switches be monitored by a physician.<sup>91</sup>

*B. The Savings from Generic Drugs vs. The "Cost" to Epilepsy Patients*

Generic drug use can help reduce the cost of prescription drugs; however, the difference in price between a brand name drug and a generic drug should not be the only cost considered.<sup>92</sup> The cost of generic prescribing includes more than just the price of the generic drug.<sup>93</sup> When the substitution causes problems, additional costs are incurred from visits to the physician and to the emergency room.<sup>94</sup> Money will also be spent on additional clinical appointments and education for patients about the changes.<sup>95</sup>

The greatest "cost," however, cannot be measured in dollars if treatment fails and a seizure occurs.<sup>96</sup> A breakthrough seizure might occur at work or while driving, and could result in the epileptic patient losing his or her job or driver's license. Moreover, the epileptic patient's life, and the lives of others, would be put at risk. Besides the physical consequences, the loss of seizure control can have a significant psychological impact on an epileptic

---

88. Heaney & Sander, *supra* note 41, at 467.

89. *Id.*

90. *Id.*

91. *Id.*

92. Crawford et al., *supra* note 26, at 169.

93. *Id.*

94. *Id.*

95. Heaney & Sander, *supra* note 41, at 467.

96. Crawford et al., *supra* note 26, at 169.



patient's lifestyle, mood, and educational opportunities.<sup>97</sup> The social consequences and personal impact of just one breakthrough seizure in a stabilized patient is so high that it could offset any money saved by a switch to generic drugs.<sup>98</sup>

### C. Treating Different Groups of Epilepsy Patients

Patients initiating antiepileptic drug therapy, patients whose epilepsy is successfully managed by antiepileptic drug therapy, and high-risk patients are all susceptible to the problems presented by generic substitution. For patients initiating antiepileptic therapy, physicians may choose between brand name and generic drugs. When establishing long-term treatment, physicians must be aware of the possibility of substitution if a brand name drug is prescribed, the multiple generic forms of a particular antiepileptic drug, and the stability of supply of both the brand name and generic drugs.<sup>99</sup> Another concern is the possibility that the patient will experience an allergic reaction to the non-active ingredients in different generic drugs.<sup>100</sup> Despite careful planning by a physician with regard to the initial prescription, it is difficult to guarantee that the patient will remain on the same drug.<sup>101</sup> In order to obtain safe, long-term treatment of epilepsy, the physician must be well-informed and the patient must be well-monitored.

The goal for patients who are well-controlled on antiepileptic drug therapy is to avoid relapse.<sup>102</sup> Patients whose epilepsy is controlled with drug therapy represent the group most affected by generic substitution and should not be switched to another drug, although the switch is sometimes

---

97. Schachter, *supra* note 49.

98. *Id.*; Heaney & Sander, *supra* note 41, at 467 (stating that despite "the willingness to accept policies of generic prescribing on the basis of cost, there is no data to quantify the overall economic benefits of switching to the cheapest available brands.").

99. Kramer et al., *supra* note 5, at 50-51.

100. *Id.* at 50.

101. See Drug Formulary, *supra* note 13; see Christensen et al., *supra* note 82, at 869; see Heaney & Sander, *supra* note 41, at 467.

102. Kramer et al., *supra* note 5, at 50.

unavoidable.<sup>103</sup> A decision to switch drugs should be planned in advance and monitored by the patient's physician.<sup>104</sup> Pharmacists must be educated about the risks associated with generic substitution as well as the importance of informing the physician and patient when making substitutions.<sup>105</sup>

Patients who are inadequately controlled on antiepileptic therapy and high-risk patient groups are more likely to be closely monitored by a physician.<sup>106</sup> However, a substitution during this stage of treatment, without the knowledge or consent of the physician, can have devastating effects. A physician cannot accurately monitor and adjust a patient's antiepileptic therapy if he or she is unaware of any changes made to the medication. Once new treatment has begun, the physician faces the same problems as when the antiepileptic drug therapy was first initiated.<sup>107</sup> If seizure control is reached, then the same issues with respect to well-controlled patients are present.<sup>108</sup> The pharmacist, the physician, and the patient need to work together to obtain stable results, regardless of which group of patients is being treated.

#### *D. Who Bears the Legal Burden of Generic Substitution of Antiepileptic Drugs?*

The legal issues related to generic substitutions are not clear.<sup>109</sup> Legal commentaries suggest that drug manufacturers' and physicians' exposure to

---

103. *Id.* at 50-51 ("For well-controlled patients with epilepsy, guidelines recommend that patients should not be switched from branded drugs to generics, between generic forms, or from generics to branded drugs due to the risk of loss of seizure control.").

104. *Id.* (suggesting patients keep a detailed diary to record the date of the switch and any seizures or unfavorable results before and after the switch); Haskins et al., *supra* note 85, at 104-05.

105. *Id.* at 50.

106. *Id.* (identifying high-risk epilepsy patients as children, the elderly, those with hepatic and renal dysfunction, those who drink and smoke, women of child bearing age, patients with comorbid conditions or taking comedication, and those with cognitive disabilities).

107. *Id.*

108. Kramer et al., *supra* note 5, at 51.

109. Heaney & Sander, *supra* note 41, at 467.

liability will remain the same.<sup>110</sup> Drug manufacturers will continue to be liable for injuries caused by defective products, and physicians are still expected to exercise reasonable care when making prescriptions for their patients.<sup>111</sup> Pharmacists, however, are taking on new responsibilities that could expose them to liability for injuries caused when generic drugs are substituted for prescribed brand name or prescribed generic drugs.<sup>112</sup> To date, there are no appellate cases finding pharmacists liable for damages caused by generic substitution. In fact, there are only two reported cases involving drug product selection, and the plaintiff in both cases was unsuccessful in establishing pharmacist liability.<sup>113</sup>

The issue is further complicated because many physicians and patients are unaware of the potential for breakthrough seizures that can occur when a pharmacist substitutes an antiepileptic medication prescribed to a controlled epileptic patient with a bioequivalent antiepileptic medication.<sup>114</sup> A study of patients and physicians revealed that both groups were not well informed regarding generic antiepileptic drugs.<sup>115</sup> Without the proper information, it is not clear whether the physician or the patient can adequately consent to a substitution.<sup>116</sup> What constitutes legally informed consent for antiepileptic substitution has not been established, nor has the burden of liability if informed consent of the physician or the patient is not obtained.<sup>117</sup> Epileptic

---

110. Christensen et al., *supra* note 82, at 869.

111. *Id.*

112. *Id.*

113. *Id.* (citing *Ullman v. Grant*, 450 N.Y.S.2d 955 (N.Y. Sup. Ct. 1982) (holding the pharmacist not liable when the physician wrote "substitution permitted" on the prescription)); *Bichler v. Willing*, 397 N.Y.S.2d 57 (N.Y. App. Div. 1977) (holding the pharmacist not liable for substituting a prescribed drug by a different manufacturer to a pregnant woman whose daughter later developed severe permanent injury due to the medication; in dicta, the court considered whether the pharmacist's choice of brands, when other brands were available, would have made a difference in determining liability).

114. *Id.*

115. Crawford et al., *supra* note 26, at 170.

116. *Id.*

117. *Id.*

patients only marginally benefit from generic antiepileptic drug substitution if they directly pay for their own medications, yet they bear the burden of any complications that may result.<sup>118</sup>

### III. LEGISLATION TO INFORM PATIENTS AND PHYSICIANS ABOUT SWITCHING TO GENERIC ANTIEPILEPTIC DRUGS

#### A. *The Epilepsy Foundation's Position on Generic Substitution*

The Epilepsy Foundation (the "Foundation") has opposed mandatory substitution of generic drugs since they first became available. In a statement posted on the Foundation's website, the Foundation stated that it "is seriously concerned about mandatory substitution of generic antiepileptic drugs without prior approval of the patient and treating physician."<sup>119</sup> The Foundation "strongly advises . . . [those] who make [medication] decisions . . . [to] address the potential adverse effects of changing from one formulation of an anti-epileptic [sic] drug to another, by *requiring the prior expressed permission* of the treating physician and the patient."<sup>120</sup>

The Foundation has focused its lobbying efforts on the FDA, Congress, and state legislatures. The Foundation has sought to have the FDA narrow the range of bioequivalence and modify the approval procedure, but has been unable to provide the evidence necessary to support its request.<sup>121</sup> Enrolling patients in major clinical trials to establish the evidence required to demonstrate that seizures are the direct effect of switches to generic antiepileptic drugs would be difficult and cost prohibitive.<sup>122</sup> Because antiepileptic drugs affect individuals differently, the few clinical trials that have evaluated therapeutic equivalence have been met with mixed results and have found difficulty proving that particular adverse events were

---

118. *Id.* (stating patients directly paying for medical costs would benefit by the lower cost of the generic medication).

119. Epilepsy Foundation, Health Care Reform: Statement on Substitution of Generic Antiepileptic Drugs, <http://www.epilepsyfoundation.org/advocacy/care/genedrev.cfm> (last visited Oct. 11, 2008).

120. *Id.* (emphasis added) (advising rulemaking bodies, medical plans, hospitals, correctional facilities, residential facilities and others who make medical decisions).

121. Rubenstein, *supra* note 34, at A1 (citing FDA's response to the alleged bioequivalence problem as: "Show us the data.").

122. *Id.*

directly attributed to generic drug substitutions.<sup>123</sup> While the results may not be conclusive, the few studies that have been conducted are compelling. A postal survey of neurologists found that, of the 289 that responded, sixty-eight percent reported breakthrough seizures and fifty-six percent reported “increased adverse events” when an epileptic patient was switched from a brand name to a generic antiepileptic drug.<sup>124</sup> Another study identified eight adult patients whose seizures not only worsened in effect but also increased in frequency after their medications were switched from the brand Phenytoin (PHT) to its generic form.<sup>125</sup> The obvious problem with conducting major clinical trials is the exposure of patients to breakthrough seizures, which is the very problem sought to be avoided.

Although the Foundation has lobbied Congress to enact legislation that will carve out an exception for antiepileptic drugs, the Foundation has focused its efforts on state legislation because states often move faster than Congress.<sup>126</sup> Patent rights for Zonegran expired in 2005, and there are already seventeen different generic manufacturers.<sup>127</sup> Four additional major brand name drugs will expire between 2008 and 2010, three of which have

---

123. Crawford et al., *supra* note 26, at 170. One study of patients treated showed 10.8% perceived problems after switching that were attributed to generic substitution. In another survey of eighty-one patients, fourteen percent reported problems when switching to a generic product. *Id.*

124. Wilner, *supra* note 31, at 996.

125. R. T. Burkhardt et al., *Lower Phenytoin Serum Levels in Persons Switched From Brand to Generic Phenytoin*, 63 *NEUROLOGY* 1494, 1494 (2004), available at <http://www.neurology.org/cgi/content/abstract/63/8/1494>. The PHT concentration on the brand name drug before generic substitution was 17.7 +/- 5.3 mg/L, which decreased to 12.5 +/- 2.7 mg/L after substitution of generic, and then increased to 17.8 +/- 3.9 mg/L after the brand name was re-introduced. *Id.* The study concluded that “brand and generic PHT do not yield equivalent concentrations in some patients and substitution should not be permitted without physician notification.” *Id.*

126. Rubenstein, *supra* note 34, at A1. “State legislation can move ‘from idea, to passage, to governor’s signature in 90 days, sometimes faster than that . . . [s]o the action is in the states.’” *Id.* (quoting Jan Faiks, director of state policy for the Pharmaceutical Research and Manufacturers of America (PhRMA)).

127. Division of Government Affairs, Epilepsy Foundation, AED Patent Exclusivity Expiration and the Number of Generic Manufacturers (2007) (unpublished, on file with author); see ORANGE BOOK, *supra* note 27, add. Patent and Exclusivity Information at 37, 38, 77, 109, 148.

generic forms already approved by the FDA.<sup>128</sup> In light of these new generic drugs and the FDA's announcement to accelerate the approval of generic drugs,<sup>129</sup> the Foundation feels it necessary to act expeditiously.

*B. State Legislation Restricting Substitution of Generic Drugs*

The Foundation is not opposed to generic drugs nor does it promote the use of brand name drugs.<sup>130</sup> Rather, the Foundation seeks to ensure that epileptic patients continue to receive the medication that works for them and to avoid substituting medications without the informed consent of both the physician and the patient.<sup>131</sup> The legislative purpose is to allow for "truly informed decision making" and to assure monitoring of potential problems.<sup>132</sup> In 2007 and 2008, twenty-four states considered some form of restriction, but only four have passed legislation: Hawaii, Tennessee, Illinois, and Utah.<sup>133</sup> The legislation passed by each of these states deserves both praise and critique.

---

128. *Id.* (Patent exclusivity expires: Depakote – 2008, Topamax – 2008, Lamictal – 2009, Trileptal – 2009); Press Release, U.S. Food and Drug Admin., FDA Approves First Generic Versions of Trileptal (Oct. 9, 2007), available at <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01721.html>.

129. AP, *FDA to Accelerate Approval of Generic Drugs: Agency Aims to Increase Number, Availability of Affordable Meds*, Oct. 4, 2007, <http://www.msnbc.msn.com/id/21137275>.

130. Bill Murphy, Director, State Gov't Relations, Epilepsy Found., Address at the Epilepsy Foundation's Annual Leadership Conference: Epilepsy Prescription Protection Legislation (Sept. 28, 2007).

131. *Id.*

132. *Id.*

133. Rockoff, *supra* note 2, at A1; Forum of America's Ideas, *supra* note 11; see Rubenstein, *supra* note 34, at A1 (stating that as of July 2007, twenty-five states had considered some form of restriction, including Hawaii, which passed legislation in 2003). Wyoming considered but failed to pass an amendment to section 33-24-148 adding section (h), which was proposed to read "A pharmacist may not substitute an anti-epileptic [sic] drug or formulation of an anti-epileptic [sic] drug, prescribed for the treatment of seizures, without the written consent of the prescribing physician." H.R. 317, 59th Leg., 636th Sess. (Wyo. 2007); see also WYO. STAT. ANN. § 33-24-148 (2007); HAW. REV. STAT. ANN. § 328-92(c) (LexisNexis 2008); 225 ILL. COMP. STAT. ANN. 85/26(c) (West 2007).

In 2003, Hawaii became the first state to pass any form of restrictive legislation on the substitution of generic antiepileptic drugs. Section 328-92(c) states, “[t]he pharmacist *shall not substitute an equivalent generic drug product* for any prescription for an anti-epileptic [sic] drug, except upon the consent of the practitioner and the patient or the patient’s parent or guardian.”<sup>134</sup> While the Hawaii state legislature should be praised for being the first to enact limitations that require the pharmacist to gain the consent of both the physician and the patient, the legislation is too restrictive. Hawaii’s drug product selection law is limited to the substitution of an “equivalent generic drug product.”<sup>135</sup> Hawaii’s statute restricts substitution of a brand name drug for a generic drug and a generic drug for a different generic version of that drug; however, the statute fails to cover the possibility that a generic drug may be substituted for a brand name drug, or a brand name drug for another brand name drug. Although these omitted substitutions are less likely to occur, it is not logical to ignore a potential substitution that can have the same catastrophic effect.

In June 2007, Tennessee passed a drug product selection law that requires a pharmacist to provide notification to the patient and the physician before substituting an antiepileptic drug, but the law does not require consent. Section 53-10-210(b) states, “[a] pharmacist . . . shall provide notification to the patient . . . before interchanging one . . . anti-epileptic [sic] drug for another . . . anti-epileptic drug [sic] . . . [and] [t]he prescriber . . . shall also be notified prior to the interchange.”<sup>136</sup> By limiting the restriction to a notification, the Tennessee statute has taken away the prescribing physician’s authority and given it to the pharmacist. Whether the patient is initiating antiepileptic therapy, is well-controlled on antiepileptic drug therapy, or is a high-risk patient, the decision regarding which medication to prescribe is best left to the person who knows and is monitoring the patient: the physician.<sup>137</sup> For example, if the patient is initiating treatment or is a high-risk patient, the physician, not the pharmacist, will know which treatments have or have not worked and which medications are the most appropriate. If the patient is a well-controlled patient, then the switch should be avoided if possible. In addition, the Tennessee statute further limits a pharmacist’s requirement to notify to “instances where the patient’s epilepsy

---

134. HAW. REV. STAT. ANN. § 328-92(c) (LexisNexis 2008) (emphasis added).

135. *Id.* § 328-92(a)(1).

136. TENN. CODE ANN. § 53-10-210(b) (Supp. 2007).

137. *See Kramer et al., supra* note 5, at 50-51.

or seizures are currently *being controlled* . . . .”<sup>138</sup> In effect, the state limits notification by a pharmacist to cases where substitution should be most avoided. If the pharmacist knows the patient is initiating treatment or is not well-controlled, the Tennessee statute allows the pharmacist to make a substitution to a drug the pharmacist finds appropriate, without notifying the physician. The law is so limited that it marginally benefits a small population of people with epilepsy.

One benefit of the Tennessee statute is its definition of “interchange.” Interchange is defined to include “substitution of a generic version for a brand version, a brand version for a generic version, or a generic version for a generic version by a different manufacturer.”<sup>139</sup> While this definition is an improvement from the definition in the Hawaii statute, it is not complete. By including “a generic version for a generic version by a different manufacturer” in its definition of interchange, the Tennessee statute leaves open the narrow possibility of a manufacturer making more than one bioequivalent generic drug. The definition of interchange also fails to consider the substitution of a brand drug for another brand drug. Like the Hawaii statute above, Tennessee fails to define all possible types of substitutions.

Illinois’ drug product selection law, passed in October 2007, *does* require a pharmacist to obtain notification *and* consent before interchange of an antiepileptic drug, but only when a “prescribing physician has indicated on the original prescription ‘dispense as written’ or ‘may not substitute’ . . . .”<sup>140</sup> In addition, the statute fails to adequately define interchange. As currently interpreted and enforced, “dispense as written” instructions only prevent switching from a brand name drug to a generic drug. A physician who specifies “dispense as written” will not prevent the pharmacist from substituting a generic drug made by one manufacturer for another generic drug made by a different manufacturer.<sup>141</sup> Without an adequate definition of

---

138. TENN. CODE ANN. § 53-10-210(b) (Supp. 2007).

139. *Id.* § 53-10-210(a)(3).

140. 225 ILL. COMP. STAT. ANN. 85/26(c) (West 2007).

When the prescribing physician has indicated on the original prescription “dispense as written” or “may not substitute,” a pharmacist may not interchange an anti-epileptic drug or formulation of an anti-epileptic drug for the treatment of epilepsy without notification and the documented consent of the prescribing physician and the patient or the patient’s parent, legal guardian, or spouse.

*Id.*

141. Murphy, *supra* note 130.



interchange, Illinois' statute only requires notification and consent when switching from a brand name drug to a generic drug.

Most recently, Utah amended its drug product equivalents law in March 2008. Like the Tennessee statute, Utah's drug product selection law only requires a pharmacist to provide notification to the physician before substituting an antiepileptic drug, but it does not require consent.<sup>142</sup> Like the Illinois drug product selection law, Utah only requires notification when the "practitioner . . . indicate[s] . . . by writing 'dispense as written' or . . . signing . . . where two lines have been printed . . . 'dispense as written' . . .".<sup>143</sup> Unlike Hawaii, Tennessee, and Illinois, Utah has a complete definition of "substitutes" (the word "interchange" is used in the Tennessee statute). "Substitutes" is defined to mean "a generic drug for another generic drug; a generic drug for a nongeneric [sic] drug; a nongeneric [sic] drug for another nongeneric [sic] drug; or a nongeneric [sic] drug for a generic drug."<sup>144</sup> Utah's drug product equivalents law clearly covers all possible types of substitutions.

A major flaw in Utah's statute, however, can be found in the last clause. Section 58-17b-605(7)(d) states that "[n]otification . . . is not required if the drug product equivalent is paid in whole or in part by Medicaid."<sup>145</sup> It seems illogical not to extend the protections of this statute to the low-income residents of Utah who are living with epilepsy. The clause singles out the group that is the least capable of financially coping if a breakthrough seizure were to occur and creates an unneeded barrier between the low-income patient and his or her prescribing physician. There is no case law interpreting the Hawaii, Tennessee, Illinois, or Utah antiepileptic statutes, and to date, no challenges have been filed.

#### IV. SUGGESTED STATUTE

##### *A. Proposed Legislation*

The proposed legislation does not prohibit substitution, but is only intended to prevent substitution without the informed consent of both physician and patient.

---

142. UTAH CODE ANN. § 58-17b-605 (7)(c) (2008).

143. *Id.* § 58-17b-605 (5)(a), 7(b).

144. *Id.* § 58-17b-605 (7)(a).

145. *Id.* § 58-17b-605 (7)(d).

(a) Definitions for use in this section:

- (1) Antiepileptic drug means (i) any drug prescribed for the treatment of epilepsy or (ii) a drug used to treat or prevent seizures.<sup>146</sup>
  - (2) Epilepsy means a neurological condition characterized by recurrent seizures.<sup>147</sup>
  - (3) Seizure means a brief disturbance in the electrical activity of the brain.<sup>148</sup>
  - (4) Substitute means the dispensing of one antiepileptic drug for a different antiepileptic drug, which includes the substitution of:
    - (i) a generic drug for a brand drug;
    - (ii) a brand drug for a generic drug;
    - (iii) a generic drug for another generic drug; or
    - (iv) a brand drug for another brand drug.<sup>149</sup>
- (b) A pharmacist, pharmacy intern or a pharmacy technician shall not substitute an antiepileptic drug or a formulation of an antiepileptic drug for the treatment of epilepsy or seizures, except upon the notification and consent of the prescribing physician and the patient or the patient's parent, legal guardian, or spouse.<sup>150</sup>

*B. The Legislation's Effect on Pharmacists and Health Care Costs*

The additional burden placed on pharmacists is minimal and not unreasonable. Any hardship created by requiring pharmacists to ask doctors and patients for permission before substituting an antiepileptic drug is outweighed by the need to assure personal and public safety. The one or two percent of the population who rely on antiepileptic medication represent a

---

146. This language is derived primarily from the language in 225 ILL. COMP. STAT. ANN. 85/26(b) (West 2007); TENN. CODE ANN. § 53-10-210(a)(1) (Supp. 2007).

147. This language is derived primarily from the language in 225 ILL. COMP. STAT. ANN. 85/26(b) (West 2007); TENN. CODE ANN. § 53-10-210(a)(2) (Supp. 2007).

148. This language is derived primarily from the language in 225 ILL. COMP. STAT. ANN. 85/26(b) (West 2007); *see also* TENN. CODE ANN. § 53-10-210(a)(4) (Supp. 2007).

149. This language is derived primarily from the language in TENN. CODE ANN. § 53-10-210(a)(3) (Supp. 2007) and the language in UTAH CODE ANN. § 58-17b-605 (7)(a) (2008).

150. *See* 225 ILL. COMP. STAT. ANN. 82/26(c) (West 2007); *see also* TENN. CODE ANN. § 53-10-210(b) (Supp. 2007). *See generally* HAW. REV. STAT. ANN. § 328-92 (2003).

small portion of the billions of dollars spent on pharmaceutical products and the volume of prescriptions dispensed by pharmacists everyday.<sup>151</sup> Pharmacists contact physicians on a regular basis about prescriptions and often talk to patients and offer their advice. There is no evidence that the proposed legislation creates an undue burden on a pharmacist to obtain permission of both the physician and the patient before substituting an antiepileptic drug.<sup>152</sup>

The proposed legislation does not require dispensing only brand name drugs or the most expensive drugs. The legislation requires the physician and the patient to be informed when a switch is suggested by the pharmacist, or encouraged or required by an insurer's drug formulary. This places the decision-making in the hands of the physician and patient to determine what is medically necessary. There is no evidence of any financial consequence to this proposed legislation. At a minimum, the legislation would save money on unnecessary doctor and emergency room visits, and further reduce the consequences of uninformed substitutions.<sup>153</sup>

## V. RECOMMENDATIONS

Experts have called on the FDA to "fund or conduct research to identify the optimum [methods] for determining bioequivalence for generic [antiepileptic drugs]."<sup>154</sup> In view of inconsistent effects of so-called bioequivalent drugs, the parameters for bioequivalence established in 1984 need to be, at the very least, reevaluated. The FDA needs to improve its monitoring of approved generic antiepileptic drugs to assure accurate reporting of adverse reactions to antiepileptic drugs.<sup>155</sup> Currently, the only reporting is voluntary. The FDA encourages epileptic patients and

---

151. Murphy, *supra* note 130.

152. *Id.* In addition, present communication systems allow a pharmacist to communicate with the physician in a variety of ways and to obtain a particular medication that is not in stock in a relatively short period of time. *Id.* As a practical effect, a burden might be placed on the patient who seeks to fill his or her prescription at night or on the weekends when his or her physician is unavailable.

153. *Id.*

154. Schachter, *supra* note 49; see also Epilepsy Foundation, An Interview with Steve C. Schachter, <http://www.epilepsyfoundation.org/generics/schachterinterview.html> (last visited Oct. 11, 2008) [hereinafter Schachter Interview].

155. Schachter, *supra* note 49; see Schachter Interview, *supra* note 154.

physicians to report breakthrough seizures on the FDA website or by calling an FDA hotline.<sup>156</sup>

Providing awareness education is an important and practical step to take. Developing programs to educate physicians and health care providers on the issues associated with antiepileptic drug substitution could reduce the risk of breakthrough seizures. Awareness education should provide guidelines outlining safety goals and risks associated with antiepileptic substitution.<sup>157</sup> The guidelines should educate physicians and health care providers on the different types of patients and the goals for each, stressing that patients whose seizures are controlled should not have their antiepileptic medication switched unless medically appropriate.<sup>158</sup> Physicians should be aware that maintaining patients on the same drug might require patients to pay more for their medications.<sup>159</sup> This will allow physicians to discuss alternatives with their patients.<sup>160</sup> If a switch is determined to be appropriate, the guidelines should educate physicians on how to properly monitor patients to achieve optimal results.<sup>161</sup>

Education programs targeting public and private payers of health insurance will facilitate the development of drug formularies and policies to

---

156. Epilepsy Foundation, Reporting Problems with Medication Switches, <http://www.epilepsyfoundation.org/generics/problems.html> (last visited Oct. 11, 2008).

157. Schachter, *supra* note 49; Haskins et al., *supra* note 85, at 104; *see* Schachter Interview, *supra* note 154; Crawford et al., *supra* note 26, at 174 (“[I]t is prudent for patients, neurologists and pharmacists to be aware of the issues and to approve generic prescribing of AEDs for certain high-risk patients prior to it being instituted.”).

158. Kramer et al., *supra* note 5, at 50-51 (“Most practice guidelines recommend that [well-controlled] patients should not be switched to another form of the drug.”); *see* Crawford et al., *supra* note 26, at 169 (stating “a patient stabilised [sic] on one AED may be at risk of that control being lost if the prescription is changed to a formulation from a different manufacturer.”).

159. *See* Kramer et al., *supra* note 5, at 46; Heaney & Sander, *supra* note 41, at 466; Crawford et al., *supra* note 26, at 169-70.

160. Schachter, *supra* note 49; Kramer et al., *supra* note 5, at 50-51; Haskins et al., *supra* note 85, at 104-05; *see* Schachter Interview, *supra* note 154.

161. Schachter, *supra* note 49; Haskins et al., *supra* note 85, at 104 (“[T]he generic substitution practice is not well understood by most patients with epilepsy and not completely understood by physicians.”); Heaney & Sander, *supra* note 41, at 465; Crawford et al., *supra* note 26, at 168; *see* Schachter Interview, *supra* note 154.

ensure patient access to antiepileptic drugs.<sup>162</sup> The goal is to have adequate protections in place to prevent mandatory substitution of antiepileptic medications. If substitution is unavoidable, for example, in the case of drug formularies, safeguards should be enacted to prevent patients from being penalized financially or overly burdened by administrative procedures if they experience treatment failure following an antiepileptic substitution.<sup>163</sup>

Awareness education should place an emphasis on informing people with epilepsy of the potential risks of switching their antiepileptic medication without medical guidance.<sup>164</sup> Many patients are unaware of these risks and may make uninformed decisions based solely on the lower costs of available generic drugs. Patients should be encouraged to discuss all antiepileptic medication switches with their physician.<sup>165</sup> Patients need to be aware of the many practical things they can do to prevent switches in their medication, such as knowing what their medication looks like and who manufactures it, so that they can monitor their medications for any unknown substitutions.<sup>166</sup>

Most importantly, “pharmacists should be educated on the unique nature of epilepsy” and the risks of antiepileptic substitution to the patient and society.<sup>167</sup> In addition, pharmacists need to be aware of the need to consult

---

162. Schachter, *supra* note 49; see Schachter Interview, *supra* note 154; *Abbott Lab.* 2005 WL 1323435, at \*15; see Drug Formularies, *supra* note 13; Parks, *supra* note 70 at 2186; see CIGNA, *supra* note 78.

163. Drug failure may require further doctor visits, emergency room visits, or a switch back to their previous medication. See Crawford et al., *supra* note 26, at 169.

164. Schachter, *supra* note 49; Crawford et al., *supra* note 26, at 167 (listing loss of driver’s license and loss of employment as social implications and risk of injury and loss of self-esteem as personal implications); see Schachter Interview, *supra* note 154; Epilepsy Foundation, Terms, <http://www.epilepsyfoundation.org/generics/glossary.html> (last visited Oct. 11, 2008); see also Spencer, *supra* note 58, at 14 (suggesting people diagnosed with epilepsy are three times more likely to commit suicide than the general population).

165. Schachter, *supra* note 49.

166. Schachter, *supra* note 49; see Schachter Interview, *supra* note 154.

167. Crawford et al., *supra* note 26, at 167-69; Schachter, *supra* note 49; Kramer et al., *supra* note 5, at 48; see also Spencer, *supra* note 58, at 14.

with physicians and the importance of exercising caution when switching among different manufacturers of the same product.<sup>168</sup>

### CONCLUSION

The bottom line is that pharmacists need to obtain notification and consent from both the patient and the patient's physician before substituting antiepileptic drugs. Generic drugs are a welcomed part of our country's health system and a necessity for keeping the cost of prescription medications down. Generic antiepileptic drugs can save numerous epileptic patients money in the end, but the administration of these drugs needs to be monitored closely. The only problematic step in the process from the physician prescribing the medication to the patient taking the antiepileptic drug is the pharmacist filling the prescription. With proper education programs and legislative safeguards in place, generic antiepileptic drugs will be more effective in producing savings to health care providers and patients.

The bioequivalence standard established by the FDA must be reevaluated for its effectiveness and applicability to generic drugs in all treatment areas. As demonstrated by antiepileptic drugs, the one-size-fits-all standard of bioequivalence is inappropriate for creating safe and effective generic drugs in all applications. The FDA's bioequivalence standard is a generic standard for generic drugs. Due to the unique nature of epilepsy and the potential danger of inaccurate medications, the archaic standard for bioequivalence has been exposed. Other medications with narrow therapeutic ranges have been shown to have similar problems. Studies on generic antidepressant drugs and generic blood thinners used to treat heart conditions also have called into question the reliability of the FDA's testing and standards for approving these types of drugs.<sup>169</sup> These studies reveal that the generic drugs reported as causing patients problems were within FDA limits of acceptability.<sup>170</sup> These studies require additional investigation by the FDA.

---

168. Schachter, *supra* note 49; Kramer et al., *supra* note 5, at 50-51; see Schachter Interview, *supra* note 154.

169. Jacqueline Stenson, *Report Questions Generic Antidepressant: ConsumerLab.com Finds Cheaper Drug May Not Work the Same as Brand*, MSNBC, Oct. 12, 2007, <http://www.msnbc.msn.com/id/21142869>.

170. See *id.* ConsumerLab.com compared the brand name antidepressant, Wellbutrin, to its FDA approved generic counter part, Budeprion, using a test-tube test and found that Budeprion dissolves faster releasing thirty-four percent of the active ingredient within the first two hours, compared to Wellbutrin that releases only eight percent in the same time period. Melinda Beck, *Inexact Copies: How Generics Differ From Brand Names*, WALL ST. J., Apr. 22, 2008, at D1. Patients switched to Budeprion reported effects ranging from tremors, headaches, anxiety and sleep disturbances, to depression and thoughts of

Legislative safeguards can be put into place to protect consumers who use generic medications, but the problem is more deeply rooted in the FDA's standard for bioequivalence.

---

suicide caused by receiving four times the active ingredient in the first two hours and not enough of the active ingredient throughout the rest of the day. *Id.*